Slide Presentation to Illustrate Laboratory and Clinical Results Presented to FDA Miscellaneous Internal Review Panel July 11, 1977

Submitted by
Thompson Medical Co.
New York, N.Y.

Ted Goons

Testimony before an FDA panel July 14, 1977 be there by 8:30 AM

5600 Fishers Lane Conf. Rm A 3rd floor ↓ go down 2 flrs

Phenylpropanolamine Versus d-Amphetamine: Effects on Appetite and on Reward Induced by Brain Stimulation in the Rat

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New York University

Thank you Dr. Steinberg,
Mr. Chairman, Members of the panel, Ladies & gentlemen,

There has been a continuous interest in suitable agents that a dieter can safely take to help reduce appetite to controllable levels. Such agents, in addition to reducing appetite, should clearly not be dependency-producing. This probably also means that they should not arouse feelings of reward or euphoria, either. At the same time they should not be psychologically aversive--at least unduly.

One such agent appears to be phenylpropanolamine according to brain stimulation studies in animals carried out in my laboratory and the laboratories of some of my colleagues, particularly Professor Hoebel whom you will hear from today. I wish to describe a study that I, with the assistance of Daniel Karron, have conducted comparing the effects of phenylpropanolamine and d-amphetamine on appetite electrically elicited from the brain with their effects on a reward system in the brain which when overactivated may result in euphoria.

In the following experiments using rats, a tiny region of the brain, the lateral hypothalamus, which controls both appetite for food and the sense of reward, was permanently implanted with an electrode and then electrically stimulated. The first slide shows one such implanted rat moving freely about while wires from the electrical stimulator are attached to its hypothalamic electrodes. You can see these electrodes sticking out from the dental cement that securely grips them to the skull. Notice how oblivious the rat seems to be of its added plumbing. Although no food is in the cage with the rat, if food were present and the current was turned on, this thoroughly satiated rat would immediately begin to eat and continue to eat as long as the current lasted.

By varying the rate at which 0.1 msec electrical pulses of a constant intensity were presented to this hypothalamic region, it was possible to vary the sense of appetite causing the eating in a finely controlled way. A few pulses per second would induce only a mild appetite while more pulses per second intensified this appetite. By presenting such electrically stimulated but satiated rats with a food composed of moistened Purina lab chow, it was thus possible to ask how many pulses per second would be necessary to get the rats to begin eating this mixture within 20 seconds after the current was turned on. Then, by comparison, how many pulses per second would be necessary when the rats were injected intraperitoneally with a range of doses of phenylpropanolamine--henceforth termed PPA? Beyond some point in the course of increasing the dose it was expected that, if PPA truly reduced appetite, then compensatorily more pulses per second than usual would be required.?/

The second slide shows the average results obtained from 4 rats. By following the ~~dark heavy~~ lines connecting the filled triangles from left to right one can

see that/at a dose of 16.5 mg/kg or greater/PPA greatly elevated the number of pulses per second of current required to induce the rats to eat. Compared to the uninjected control results shown by connected open triangles, this increase proved statistically significant. Obviously PPA reduces appetite at these doses since, by way of compensation, the electrical stimulation of appetite had to be so greatly increased. Even at the lower doses of $1.6^{5}_{\wedge}$ and $8.2^{5}_{\wedge}$, a one-tailed t-test of the difference between drug and control conditions proved significant, again supporting the view that PPA is an appetite suppressant.

Now let us turn to the question as to whether or not PPA is safe to use in terms of possible euphoragenic effects that might lead to the development of drug dependency. To understand how we answered this question it is necessary to know that rats will voluntarily press down a lever to self-administer brief bursts of current to the reward system that runs through the same lateral hypothalamic region involved in controlling appetite. Thus, by using much the same stimulation procedure as in testing appetite, that is say, by varying the rate at which 0.1 msec electrical pulses of a constant intensity were presented, it was possible to vary the sense of reward in a finely controlled way. By arranging it so that each time a rat pressed the lever he obtained a quarter-second train of pulses, it was possible to ask how many pulses in this train it would take to reward the rat enough to press the lever at least 20 times a minute. What then would be the effect of PPA at different doses on the number of pulses required?

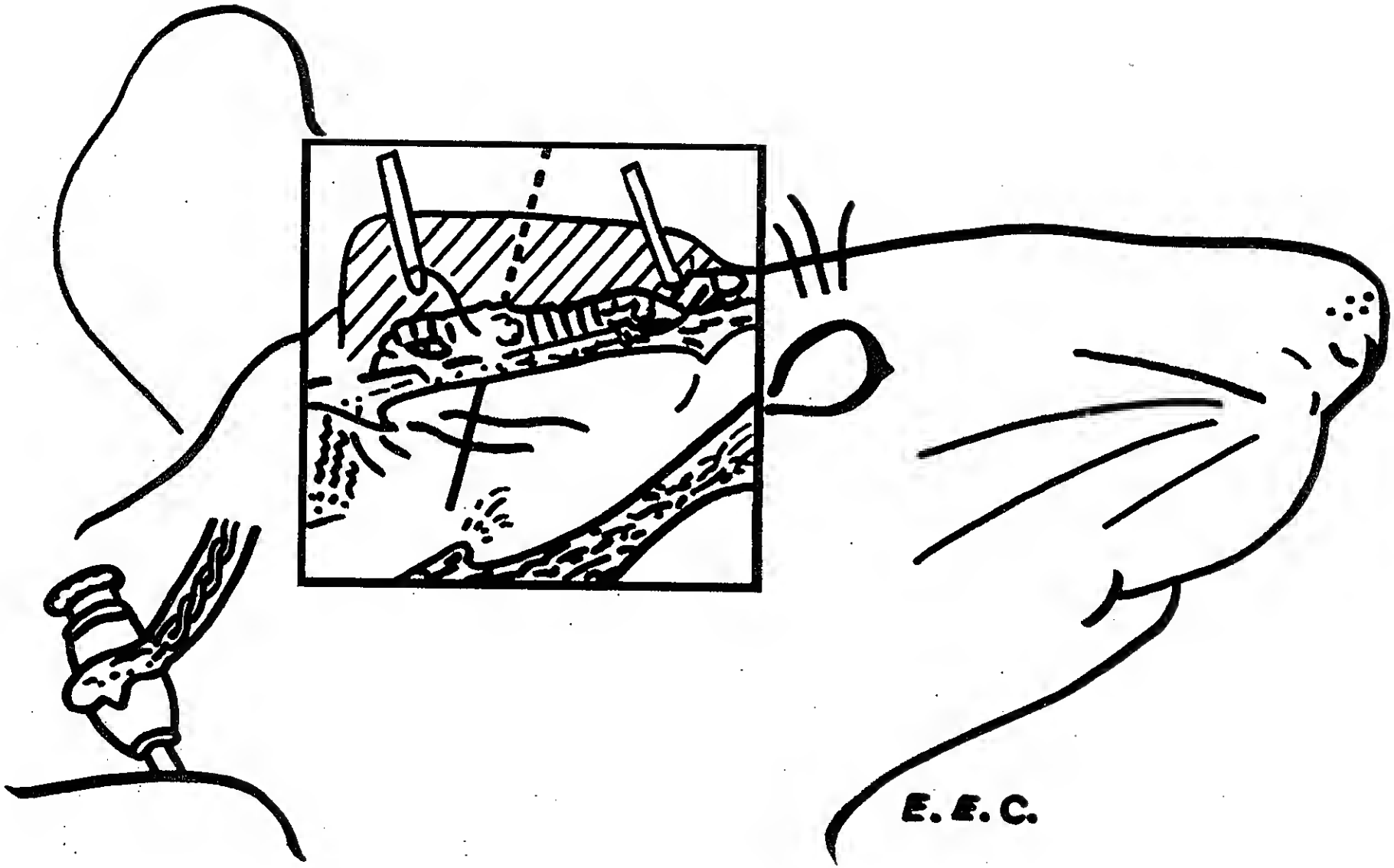
The third slide portrays the average results, again, in the same 4 animals. By following the ~~heavy~~ dotted line connecting the filled circles from left to right and by comparing this PPA line with the control line lying generally below, one can see that the number of pulses required to be rewarding certainly did not decrease as PPA dose increased and may have increased although by no means as

much as in the appetite test. This compensatory increase in the pulses per second required to keep the rats lever pressing in the drug condition, particularly at the higher doses, means that PPA did not increase but rather, if anything, reduced reward--a fact more strongly evidenced by results Professor Hoebel will report.

By contrast, as shown in the last slide, a 2-mg/kg dose of d-amphetamine, containing far fewer molecules than any but the smallest dose of PPA, greatly decreased the amount of current required to be rewarding. However, at the same time this drug, like PPA, greatly increased the current necessary to elicit eating. From this we can conclude that, while d-amphetamine markedly suppressed appetite--even at lower doses than required for PPA, it also markedly potentiated reward--perhaps even to a euphoric level. By comparison, no dose of PPA potentiated reward although PPA too decreased appetite.

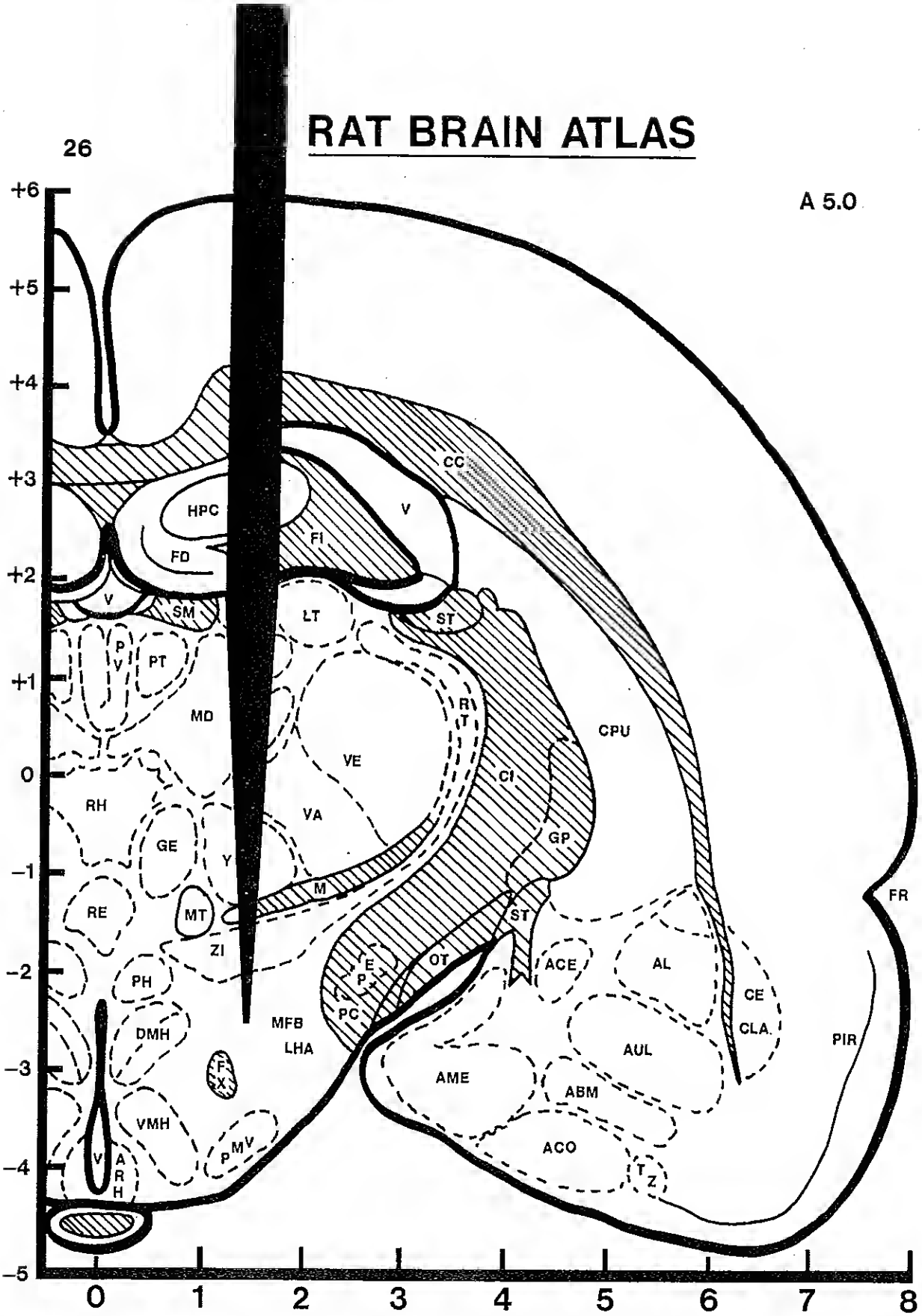
In summary then, this study strongly suggests that, although phenylpropanolamine is apparently weaker molecule for molecule than d-amphetamine, it is nevertheless an effective and much safer appetite suppressant. It does not have the rewarding or euphoragenic side effects that, in terms of the dangers of leading to drug dependency, have compromised d-amphetamine's usefulness in reducing appetite. Yet, like d-amphetamine, phenylpropanolamine can be used to help harness an unruly appetite to the willpower of the earnest dieter.

TC-1

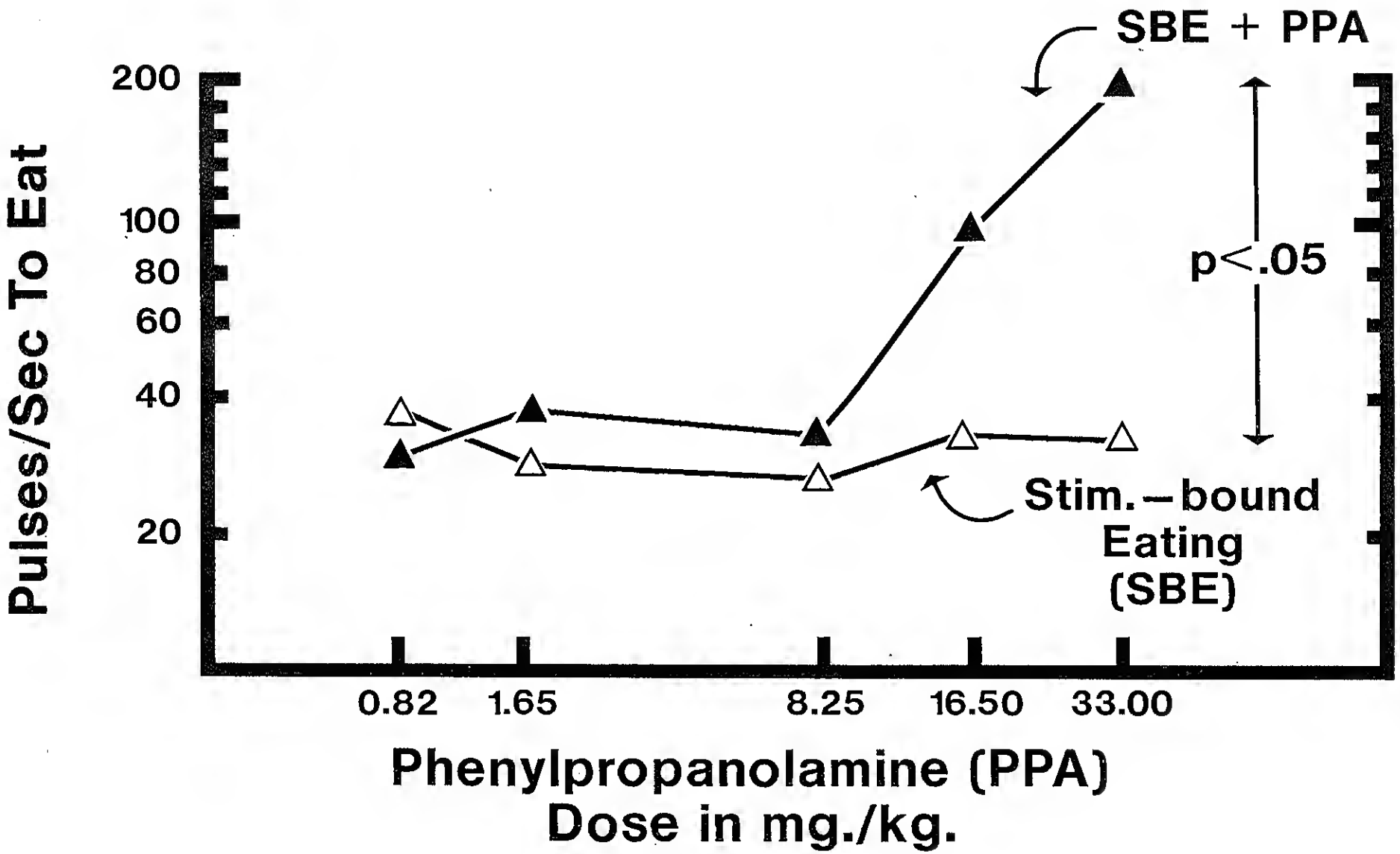


TC—H1

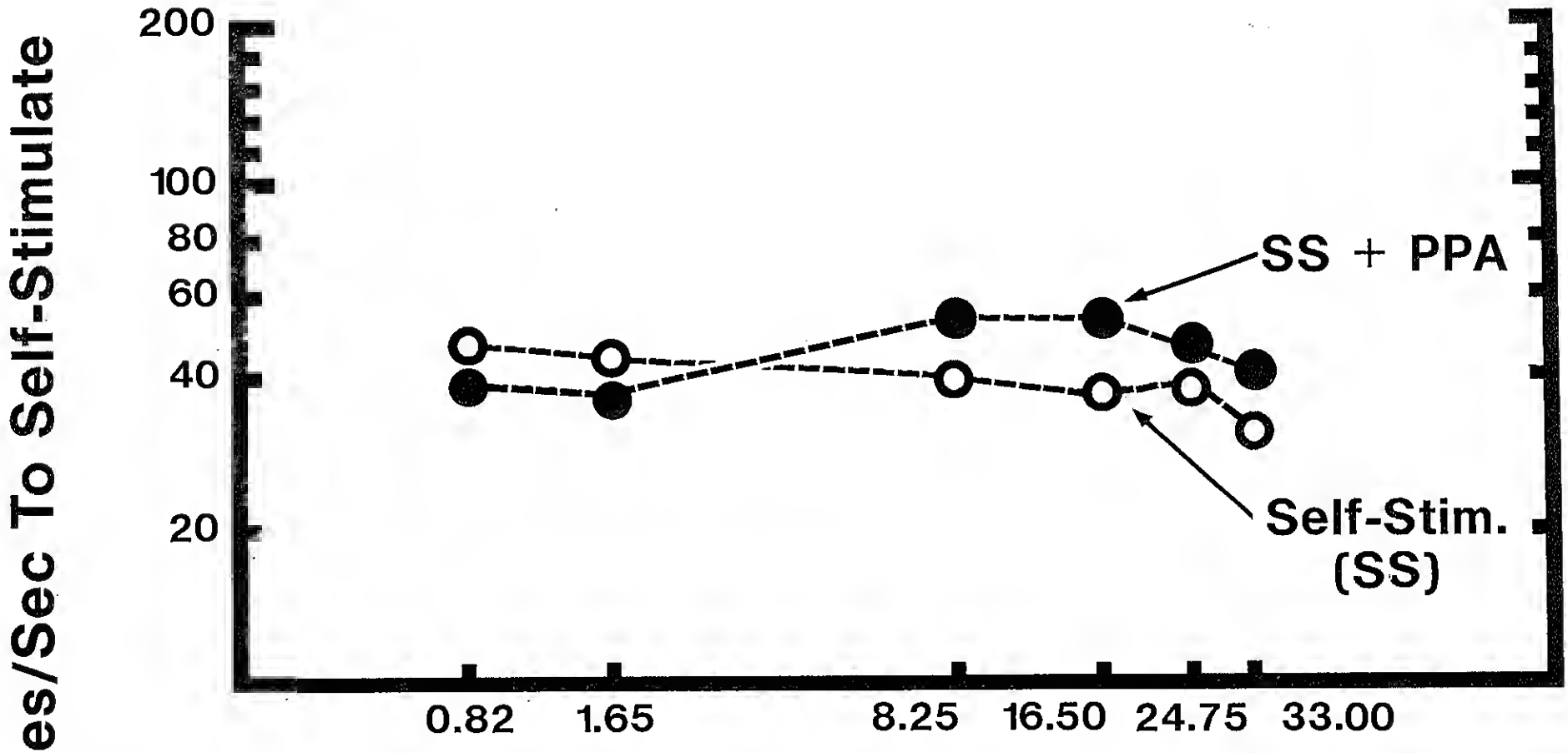
RAT BRAIN ATLAS



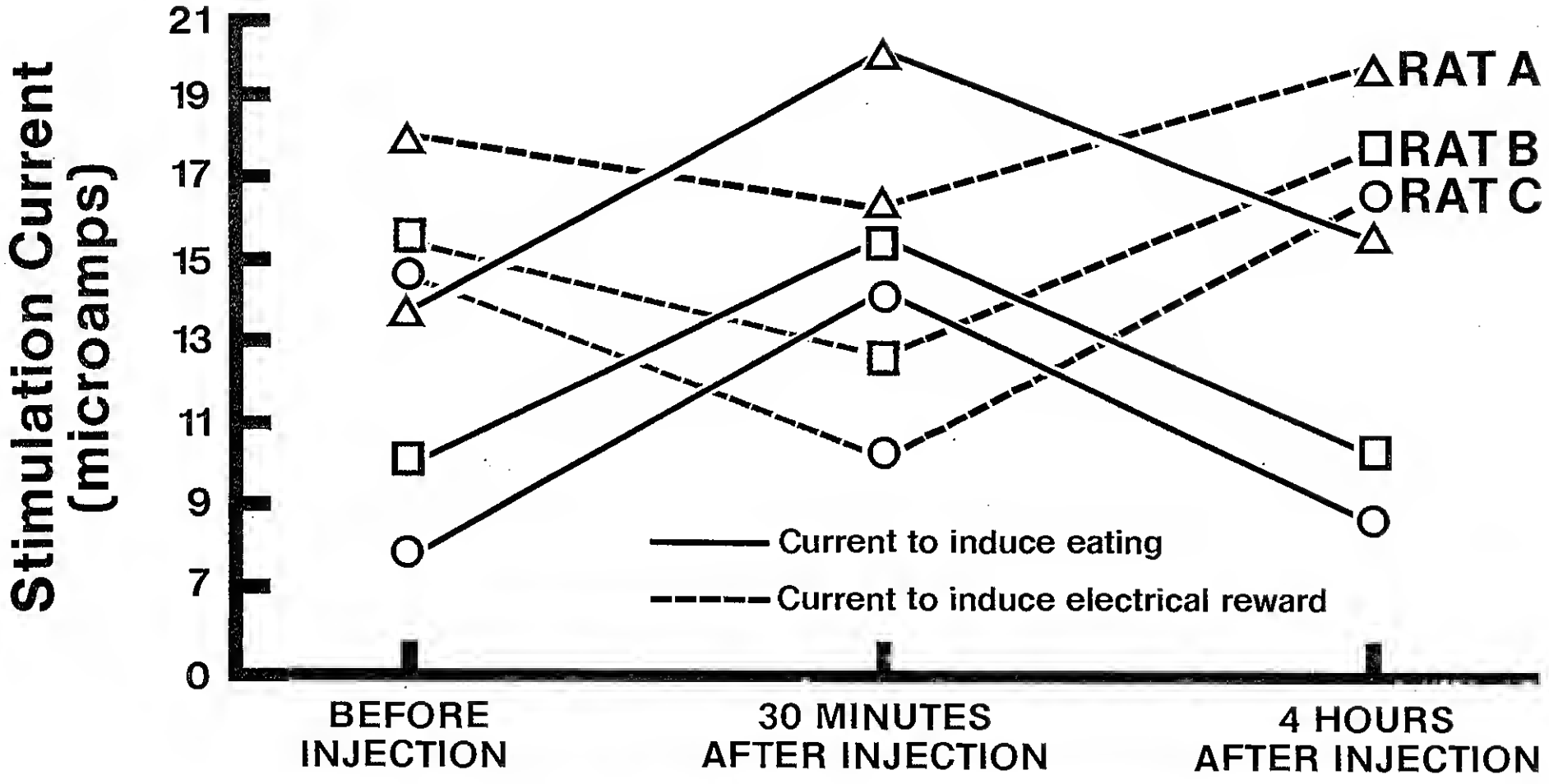
TC—H2


SBE + PPA
200
100
80
60
40
20
Pulses/Sec To Eat
p<.05
Stim.–bound
Eating
(SBE)
0.82
1.65
8.25
16.50
33.00
Phenylpropanolamine (PPA)
Dose in mg./kg.

TC–2


Pulses/Sec To Self-Stimulate
200
100
80
60
40
20
SS + PPA
Self-Stim.
(SS)
0.82
1.65
8.25
16.50
24.75
33.00
Phenylpropanolamine (PPA)
Dose in mg./kg.

TC—3



d-Amphetamine (2 mg./kg.)

TC—4